REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the present amendment and following remarks. Claims 19 and 21 are pending and under consideration. Claim 21 has been amended and claims 22 and 23 have been added to more clearly describe certain aspects of the invention. It is urged that support for the above amendments can be found throughout the specification as originally filed and that none of the amendments constitutes new matter. This amendment is not to be construed as acquiescence to any rejection and is made without prejudice to the prosecution of any subject matter modified by the amendment in a related divisional, continuation, or continuation-in-part application.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT

Claims 19 and 21 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not adequately enabled by the instant specification. The Examiner asserts that the specification fails to teach the skilled artisan how to make or use the full scope of the claimed invention without undue experimentation. More specifically, the Examiner alleges that the specification does not identify the vitamin B_{12} binding sites on TcII, and, therefore, the identification of antibodies possessing the claimed characteristics would require screening using apo-TcII, which would fail to distinguish between antibodies having agonist versus antagonist function. Furthermore, the Examiner alleges that the application fails to disclose assays for all of the functional information recited in the claims, including directed to the vitamin B_{12} binding site on TcII, growth blocking, and antagonizing or modulating the binding site.

Applicants respectfully traverse this basis of rejection and submit that the specification adequately teaches the skilled artisan how to make and use the claimed invention. Applicants further submit that the production and screening of growth blocking agents directed to a vitamin B_{12} binding site on TcII and capable of inhibiting cellular uptake of vitamin B_{12} would require merely routine methods and assays, which are described in detail in the instant specification and which are widely known in the art.

As an initial matter, Applicants strongly disagree with the Examiner's apparent conclusion that the identification of specific amino acid residues of TcII required for binding to vitamin B_{12} is necessary in order for the skilled artisan to produce antibodies directed to the vitamin B_{12} binding site on TcII. To the contrary, Applicants submit that the identification of antibodies that bind to a functional region of a polypeptide is most readily accomplished via functional assays. The skilled artisan would readily appreciate that binding regions on polypeptides are frequently conformation-dependent and that the production or screening of antibodies using only a small region of the polypeptide comprising amino acid residues implicated in binding may fail to produce or identify antibodies that bind to the binding domain in its native conformation within the entire polypeptide. Accordingly, functional assays utilizing full or nearly full-length polypeptides provide the most reliable means to identify antibodies that bind to a functional region of a polypeptide. Applicants submit that the instant application clearly teaches the skilled artisan how to produce antibodies against recombinant TcII and identify antibodies that bind to the vitamin B_{12} binding site on TcII. For instance, Example 8 teaches the production of recombinant TcII, and Example 9 teaches the production and screening of antibodies against TcII, including the identification of antibodies that bind the vitamin B_{12} binding site of TcII, as demonstrated by their ability to block binding of vitamin B_{12} to TcII. As additional support of these statements, Applicants submit the accompanying Declaration of Dr. Edward V. Quadros, an expert in the field, which further establishes that the instant specification provides sufficient enabling disclosure to teach the skilled artisan how to make and use the antibodies possessing the claimed characteristics.

Regarding the Examiner's concerns that the skilled artisan would be unable to distinguish antibodies having antagonist versus agonist function, Applicants submit that the skilled artisan would appreciate that antibodies that inhibit the binding of vitamin B_{12} to TcII would clearly possess this claimed antagonist function. Furthermore, these antibodies would also be expected to possess related antagonist functions, since it is understood that vitamin B_{12} must be complexed to TcII in order to enter cells via the vitamin B_{12}/TcII-specific receptor. As described in the instant application on page 2, lines 3-4, the vitamin B_{12}/TcII receptor recognizes only the vitamin B_{12}/TcII complex and not the transport protein or vitamin alone. In addition,

Applicants submit that the identification of antibodies that bind the vitamin B_{12} binding site on TcII and possess the claimed characteristics of inhibiting cellular uptake of vitamin B_{12} and blocking cell growth are readily identified using routine methods, including those described in the instant application. For example, methods of identifying monoclonal antibodies that inhibit cellular uptake of vitamin B_{12} are described in Example 10, and methods of identifying monoclonal antibodies that inhibit cell growth are described in Examples 12 and 16. Thus, the instant application provides assays for all of the recited functional attributes of the claimed antibodies. Thus, Applicants submit that the skilled artisan could readily identify antibodies having the claimed characteristics.

In light of these remarks and the accompanying Declaration of Dr. Edward V. Quadros, Applicants respectfully request that this basis of rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, INDEFINITENESS

Claims 19 and 21 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. More specifically, the Examiner alleges that the instant application does not teach the metes and bounds of the vitamin B_{12} binding site on TcII and that the meaning of "antagonizing or modulating said binding site" is unclear, because the terms antagonize and modulate refer to functions, not sequences or sites.

Applicants respectfully traverse this basis of rejection and submit that the skilled artisan would readily understand the metes and bounds of the claimed invention. As a first matter, Applicants submit that the skilled artisan would clearly understand that the claimed antibodies bind to a specific region of TcII, namely the vitamin B_{12} binding site and that antibodies having this characteristic could be readily ascertained by performing a routine assay, such as that described in Example 9. Furthermore, Applicants note that even if the specific amino acid residues making up the vitamin B_{12} binding site on TcII were identified, it would be highly unlikely that the skilled artisan could determine if any particular antibody bound to this site without performing such a binding assay. Thus, it is considered routine to screen antibodies to determine if they possess a claimed functional characteristic. Applicants also note that new

claims 22 and 23 do not recite this particular characteristic and, therefore, are not subject to this particular basis of rejection.

Applicants further submit that the skilled artisan would understand the meaning of the phrase, "antagonizing or modulating said binding site." However, without acquiescence to this basis of rejection and solely to expedite prosecution, Applicants have amended claim 21 to more clearly indicate that the claimed antibody inhibits binding of vitamin B12 to its biding site on TcII.

Applicants submit that the meaning of the claims is clear and definite and respectfully request that the Examiner reconsider and withdraw these bases of rejection, in light of these amendments and comments.

REJECTIONS UNDER 35 U.S.C. § 102(B)

Claims 1, 2, 3, 4 and 19 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Quadros *et al.*, published December 1-5, 1995. More specifically, the Examiner alleges that Quadros *et al.* teaches monoclonal antibodies that bind at or near the vitamin B_{12} binding site on apo TcII, block vitamin B_{12} binding to apo TcII, and decrease the uptake of vitamin B_{12}.

Applicants respectfully traverse this basis of rejection and submit that Quadros *et al.* fails to anticipate the claimed invention.

As an initial matter, Applicants submit that Quadros *et al.* does not qualify as prior art under 35 U.S.C. § 102(b), since it was not published more than one year prior to the priority date of January 11, 1996 that was acknowledged by the Examiner for the instant application in the Office Action mailed June 10, 2002. Accordingly, Quadros *et al.* was published only approximately one month prior to the acknowledged priority date of the instant application and does not qualify as prior art under 35 U.S.C. § 102(b).

Although the claims are not currently rejected under 35 U.S.C. § 102(a), Applicants further submit that Quadros *et al.* is not prior art under Section 102(a), since it was not published prior to the priority date of the instant application. The instant application claims priority to U.S. Application Nos. 07/880,540, 08/306,540, 08/381,552, 08/476,440, and

08/584,949. However, in the Office Action mailed June 10, 2002, the Examiner denied the majority of Applicant's priority claims and only afforded the instant application the filing date of U.S. Patent Application No. 08/584,949, January 11, 1996, as its priority date. Without acquiescing to the Examiner's conclusions regarding the appropriateness of Applicants' priority claim to the other applications, Applicants respectfully request that the Examiner reconsider her denial of priority to U.S. Patent Application No. 08/476,440, filed June 7, 1995, and acknowledge the instant application's right to priority to this application. The specification of U.S. Patent Application No. 08/476,440 is identical to the specification of U.S. Patent Application No. 08/584,949, for which priority was recognized. Accordingly, U.S. Patent Application No. 08/476,440 also provides sufficient support for the presently claimed invention, and the instant application should clearly be awarded the filing date of this application, June 7, 1995, as a priority date. Applicants note that this date is prior to the publication date of Quadros *et al.*, December 1-5, 1995, so Quadros *et al.* does not qualify as prior art under 35 U.S.C. § 102(a).

In addition, even assuming *arguendo* that Quadros *et al.* qualified as prior art under Section 102, Applicants respectfully submit that Quadros *et al.* fails to disclose antibodies having each of the claimed features and, consequently, fails to anticipate the presently claimed invention. The instant claims recite the characteristic that the antibodies block growth. However, Quadros *et al.* fails to describe antibodies that bind to the vitamin B_{12} binding site on TcII and inhibit cell growth. Specifically, Quadros *et al.* state that their monoclonal antibodies that bind TcII at or near the vitamin B_{12} binding domain did not affect cell replication and did not cause a prolongation of cell doubling time. Thus, the monoclonal antibodies described by Quadros *et al.* as binding at or near the vitamin B_{12} binding site on TcII failed to block growth and, accordingly, do not anticipate the instant claims.

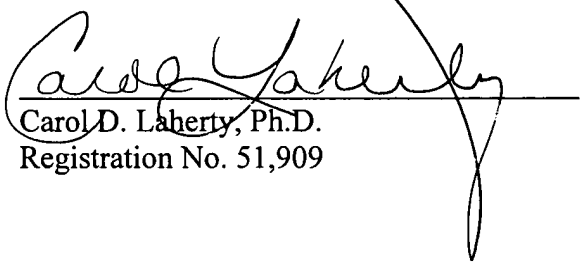
In light of the above comments, Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. Applicants have made every effort to place the application in condition for allowance. However, should any remaining issues exist, the Examiner is kindly requested to contact the undersigned attorney at (206) 622-4900.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	A. Charles Morgan, Jr. et al.
Application No.	:	09/654,116
Filed	:	August 30, 2000
For	:	GROWTH BLOCKING AGENTS
Examiner	:	Patricia A. Duffy, Ph.D.
Art Unit	:	1645
Docket No.	:	180042.418C2
Date	:	January 7, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF EDWARD V. QUADROS, PH.D.

The undersigned, Dr. Edward V. Quadros, hereby declares:

1. I am currently an Associate Professor in the Departments of Medicine and Biochemistry at the State University of New York Health Science Center and a co-inventor of the subject matter disclosed in the above-identified application.

2. I have read and understood the above-identified application and submit this Declaration for the purpose of providing evidence that a person of ordinary skill in the relevant art, based upon the teachings of this application and the general knowledge in the field, could readily produce the claimed antibodies.

3. As an initial matter, I submit that the application provides sufficient instruction and guidance to enable one of ordinary skill in the art to produce monoclonal antibodies having the same properties as those described and claimed in the application, even if exactly the same monoclonal antibodies as those specifically described in the application are not obtained. More specifically, the application provides detailed instruction regarding the production of monoclonal antibodies directed to transcobalamin II (TcII), including methods of producing recombinant TcII to be used as immunogen (Example 8) and methods of producing and identifying monoclonal antibodies directed to

a Vitamin B12 binding site on TcII (Example 9). Furthermore, the application provides detailed methods for identifying monoclonal antibodies directed to the Vitamin B12 binding site on TcII that possess the claimed characteristics of inhibiting cellular uptake of Vitamin B12 and blocking cell growth. Specifically, Example 10 describes methods of identifying monoclonal antibodies that inhibit cellular uptake of Vitamin B12, and Examples 12 and 16 describe methods of identifying monoclonal antibodies that inhibit cell growth. Accordingly, I submit that one of ordinary skill in the art, based upon the guidance provided in the application and general knowledge in the field, would be able to readily produce monoclonal antibodies to TcII and identify those directed to a Vitamin B12 binding site on TcII that are capable of inhibiting cellular uptake of vitamin B12 and blocking cell growth without undue experimentation or difficulty.

4. Furthermore, I submit that the skilled artisan would have every expectation that monoclonal antibodies produced and identified according to the methods described in the application would possess the claimed characteristics based, at least in part, on the description of the successful production of such antibodies provided in the Examples of the application. According to the application, the method described in Example 9 was used to successfully identify a number of monoclonal antibodies directed to the Vitamin B12 binding site on TcII, as illustrated in Figure 5. Furthermore, the method described in Example 10 was used to successfully identify monoclonal antibodies directed to TcII that inhibited cellular uptake of Vitamin B12, as shown in Figure 6. I further submit that the skilled artisan would immediately recognize that antibodies that inhibit the binding of Vitamin B12 to TcII would necessarily inhibit cellular uptake of Vitamin B12, since it is well known in the art, as described in the instant application, that Vitamin B12 uptake is mediated by TcII via the TcII receptor. Based on this understanding and the evidenced success at producing monoclonal antibodies having the claimed characteristics, I submit that one of ordinary skill in the art would be able to similarly produce monoclonal antibodies having these characteristics without difficult or undue experimentation, based solely on the teachings of the application and general knowledge in the art.

5. In summary, upon review of the patent application, I readily conclude that monoclonal antibodies having the claimed features could be readily produced by a person

of ordinary skill in the art based solely on the instruction provided in the application and general knowledge in the field.

6. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful, false statements, and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Edward V. Quadros, Ph.D.

Jan 8th, 2004
Date